



The Satisfactory Analgesia and Minimal Emesis of Elderly Patients After Thoracoscopic Lung Surgery: Oliceridine versus Sufentanil in a Randomized Controlled Trial

Yongliang Cai, Yihao Jiang, Qingwei Zhang, Jianjun Yang , Zhongyun Wang*, Heliang Sun 

Department of Anesthesiology and Perioperative Medicine, The First Affiliated Hospital with Nanjing Medical University, Nanjing, 210000, People's Republic of China

*These authors contributed equally to this work

Correspondence: Heliang Sun; Zhongyun Wang, Department of Anesthesiology and Perioperative Medicine, The First Affiliated Hospital with Nanjing Medical University, No. 300, Guangzhou Road, Nanjing, Jiangsu, 210000, People's Republic of China, Email njmu528@163.com; zywang1970@126.com

Purpose: To compare oliceridine with sufentanil for the proportion of elderly patients achieving satisfactory analgesia with minimal emesis (SAME) after thoracoscopic lung surgery.

Methods: This prospective, double-blind, randomized controlled trial enrolled elderly patients aged 65–80 years scheduled for thoracoscopic lung surgery to receive patient-controlled intravenous analgesia with either oliceridine or sufentanil. The primary outcome was the proportion of patients achieving SAME within the first 3 postoperative days, defined as a daily average coughing numerical rating scale (NRS) pain score < 4 and daily highest postoperative nausea and vomiting (PONV) score < 2. The secondary outcomes included NRS pain scores, rescue analgesia, 15-item Quality of Recovery (QoR-15) scores, safety outcomes, time to ambulation, and postoperative length of stay.

Results: Among the 247 patients analyzed, oliceridine was associated with a higher proportion of patients achieving the SAME endpoint within the first 3 postoperative days compared with sufentanil (46.3% vs 32.3%; $P = 0.023$). Furthermore, the patients with oliceridine demonstrated lower NRS scores on POD1 (3.6 ± 1.9 vs 4.4 ± 2.1 ; $P = 0.018$) and POD2 (3.2 ± 1.2 vs 3.7 ± 1.3 ; $P = 0.039$), less requirement for rescue analgesia ($P = 0.021$), and higher QoR-15 scores on POD1 ($P < 0.001$) and POD2 ($P = 0.010$). Oliceridine also reduced the time to first ambulation (19 h [16, 22] vs 22 h [18, 25]; $P < 0.001$). No significant difference was observed in postoperative length of stay or safety outcomes.

Conclusion: Oliceridine, compared with sufentanil for postoperative analgesia, increased the proportion of achieving SAME within the first 3 PODs, provided better analgesia, and improved postoperative recovery quality with comparable safety outcomes for elderly patients undergoing thoracoscopic lung surgery.

Trial Registration: www.chictr.org.cn, ChiCTR2500102213.

Keywords: oliceridine, sufentanil, SAME, QoR-15, thoracoscopic lung surgery

Introduction

Video-assisted thoracoscopic surgery (VATS) is a widely adopted minimally invasive procedure characterized by reduced trauma and faster recovery.^{1–3} Nevertheless, postoperative pain remains a significant concern following VATS, with over half of patients experiencing moderate to severe acute pain,⁴ and approximately 25–50% developing chronic post-surgical pain.⁵

Patient-controlled intravenous analgesia (PCIA) is recommended by the American Pain Society as a primary approach for postoperative analgesia,⁶ and it can be combined with intercostal nerve blocks to form an effective

multimodal analgesia regimen in VATS.^{7,8} Opioids serve as the core therapeutic agents in PCIA due to their potent analgesic effects. Among these, sufentanil has gained increasing utilization for postoperative analgesia owing to its rapid onset and manageable safety profile.^{7,9} Nevertheless, it still carries a significant risk of opioid-related adverse events, especially postoperative nausea and vomiting (PONV), which occurs in over 30% of patients even with prophylactic measures.¹⁰

Elderly patients exhibit unique physiological vulnerabilities following VATS. Age-related reductions in respiratory muscle strength and impaired cough clearance predispose elderly patients to sputum retention, atelectasis, and pulmonary infection.¹¹ Postoperative cough-associated pain further suppresses effective expectoration, exacerbating these risks. Although opioids provide potent analgesia, opioid-induced nausea and vomiting (OINV) often lead to premature dose reduction or discontinuation, resulting in inadequate pain control.¹² Consequently, patients avoid coughing due to pain, which impairs sputum clearance and increases the risk of pulmonary complications. Additionally, elderly patients often exhibit declined swallowing function and airway protective reflexes, rendering them more susceptible to aspiration pneumonia secondary to OINV,¹³ while age-related declines in hepatic, renal, and respiratory function further predispose them to opioid-related respiratory depression.¹⁴ Thus, an analgesic that effectively controls cough-related pain while minimizing opioid-related adverse events is essential for optimizing outcomes in this population.

Mechanistically, conventional opioids exert analgesia via μ -opioid receptor activation, engaging both the analgesic G protein pathway and the β -arrestin pathway linked to adverse events,^{15,16} such as respiratory depression, nausea and vomiting, and gastrointestinal dysfunction. In contrast, oliceridine, a novel US FDA-approved (August 2020) G protein-biased μ -opioid receptor agonist for moderate to severe acute pain, exhibits biased agonism that markedly reduces β -arrestin recruitment,^{17,18} theoretically, offering a safer profile for vulnerable patients. However, the therapeutic potential of oliceridine for elderly VATS patients remains unexplored.

The satisfactory analgesia with minimal emesis (SAME) is a clinically meaningful composite endpoint that has been previously applied in VATS patients,^{19,20} which can balance the benefits of G protein pathway mediated analgesia and β -arrestin-mediated adverse events. Therefore, we conducted this randomized controlled trial to compare the efficacy of PCIA with oliceridine versus sufentanil using the composite endpoint of SAME in elderly VATS patients.

Materials and Methods

Ethical Statements

This study (2024-SR-793) was approved by the Ethics Committee of The First Affiliated Hospital with Nanjing Medical University in accordance with the Declaration of Helsinki. Informed consents were obtained from all enrolled patients. The trial was registered with the Chinese Clinical Trial Registry (www.chictr.org.cn, ChiCTR2500102213).

Criteria for the Subjects

Patients aged 65–80 years with ASA physical status II or III, BMI 18–30 kg/m², scheduled for elective video-assisted thoracoscopic lobectomy or segmentectomy were included in this study. Exclusion criteria included hepatitis, renal dysfunction, severe cardiovascular or cerebrovascular disease, chronic pain, mental illness, hypersensitivity to study medications, regular use of sedatives or analgesics, inability to read, write or comprehend, intraoperative blood loss \geq 800 mL, conversion to thoracotomy, and postoperative admission to ICU.

Randomization and Blinding

An independent statistician generated the randomization sequence using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) with permuted blocks of 4, to achieve 1:1 allocation to the oliceridine or sufentanil group. Allocation was sealed in sequentially numbered opaque envelopes controlled by investigators who were not involved in data acquisition or study implementation. After surgery began, the coordinator opened the envelopes and prepared the PCIA pump with the assigned study drug (oliceridine or sufentanil). All pumps were labeled only as “trial drug” to ensure visual uniformity and were delivered to the anesthesiologists before the end of surgery. All patients, healthcare team members, and outcome assessors were therefore blinded to treatment allocation.

Anesthesia and Interventions

Before surgery, patients adhered to a standard preoperative fast of 6 h for solids and 2 h for clear fluids and received instructions on the PCIA pump and the Numerical Rating Scale (NRS) for pain assessment.

In the operating room, standard monitoring was applied, including electrocardiography, pulse oximetry (SpO₂), invasive arterial blood pressure, end-tidal CO₂, and nasopharyngeal temperature. Bispectral index was used to monitor depth of anesthesia. General anesthesia was induced with i.v. midazolam 0.04 mg/kg, ciprofol 0.3 mg/kg, sufentanil 0.4 µg/kg and cisatracurium 0.2 mg/kg. Double-lumen endotracheal intubation was performed for mechanical ventilation (Dräger Fabius® Plus, Germany). Ventilator parameters were set as tidal volume 5–8 mL/kg, PEEP 5 cmH₂O, and were adjusted to maintain SpO₂ ≥ 95% and an end-tidal CO₂ 35–45 mmHg. Anesthesia was maintained with a continuous intravenous infusion of propofol 2–5 mg/kg/h, remifentanil 0.1–0.3 µg/kg/min, and sevoflurane 1–3% titrated to maintain BIS between 40–60. Cisatracurium was administered intermittently based on surgical requirements. Intraoperative blood pressure fluctuation was maintained within 20% of baseline values, and nasopharyngeal temperature was kept above 36 °C. Moreover, dexamethasone 5 mg and ondansetron 8 mg were routinely administered during anesthesia to prevent PONV. Prior to wound closure, the intercostal nerve block under direct thoracoscopic vision was performed by the same designated surgeon with 20 mL of 0.66% liposomal bupivacaine at T4 to T7 intercostal space. A independent nurse then connected them to the PCIA pump according to their group assignment after the patient had fully emerged from anesthesia. Moreover, flurbiprofen axetil 50 mg was administered intravenously twice daily for the first 3 postoperative days (PODs). The patients were randomized to one of the following PCIA program: The oliceridine group received 20 mg oliceridine diluted in 100 mL 0.9% saline, while the sufentanil group received 100 µg sufentanil prepared similarly in 100 mL 0.9% saline. The pump parameters were standardized across both groups, comprising 2 mL bolus (oliceridine 0.4 mg or sufentanil 2.0 µg), 10-minute lockout time, and background infusion of 1 mL/h (oliceridine 0.2 mg/h or sufentanil 1.0 µg/h). Earlier studies indicate that the analgesic potency of oliceridine is approximately 5 times that of morphine,²¹ whereas sufentanil is 1000 times stronger.²² Consequently, the dose ratio of sufentanil to oliceridine was calculated to be 1:200.²³

Postoperative pain was assessed using the NRS (11-point scale: 0 [no pain], 0 < NRS < 4 [mild pain], 4 ≤ NRS < 7 [moderate pain], 7 ≤ NRS < 10 [severe pain], 10 [worst pain imaginable]). Rescue analgesia with dezocine 5 mg iv. was administered if the patient had a NRS score ≥ 4 or complained of pain even after a PCIA bolus. The PONV score was defined as follows: 0 = no nausea, 1 = mild nausea (no treatment needed), 2 = moderate nausea or retching (may need treatment), 3 = frequent vomiting (controlled with antiemetics), and 4 = severe vomiting (uncontrolled with antiemetics). Rescue antiemetic therapy with additional ondansetron 8 mg i.v. was administered to patients who had a PONV score ≥ 2.

Study Outcomes

The primary outcome was the proportion of patients achieving SAME within the first 3 PODs, defined as a daily average NRS score during coughing (assessed at 8-h intervals) < 4 and daily highest PONV score < 2.¹⁹ Secondary outcomes included the NRS scores during coughing, 15-item Quality of Recovery (QoR-15) scale scores (ranging from 0 to 150, with higher score indicating better postoperative recovery) on POD1–3, the incidence of nausea and vomiting, number of PCIA bolus, and incidence of rescue analgesics within the first 3 PODs, time to ambulation, postoperative length of stay, patient satisfaction score (ranging from 0 [worst] to 5 [best]) for postoperative PCIA, and safety outcomes (including constipation, dizziness, pruritus, urinary retention, severe sedation, and severe respiratory depression) within the first 3 PODs.

Sample Size Calculation

In our pilot study involving 30 patients (15 per group), the observed SAME rates were 60% in the oliceridine group (9/15) and 40% in the sufentanil group (6/15). Based on these preliminary data, a sample size of 99 participants per group was calculated using PASS (version 15.0.5; NCSS, LLC, Kaysville, Utah, USA) for a two-group comparison, providing

80% statistical power at a two-tailed significance level of $\alpha = 0.05$. To account for potential 20% dropout rate, the final sample size was set to 248 patients, with 124 in each group.

Statistical Methods

The Per-protocol set (PPS) analysis was used to compare the SAME endpoint between oliceridine and sufentanil under standardized conditions, minimizing confounding from protocol deviations and non-adherence. For continuous variables, data are presented as mean \pm standard deviation (SD) or median (Quartile 1, Quartile 3) according to the normality of distribution; for categorical variables, data are presented as number (%).

Group differences between the oliceridine and sufentanil groups were examined using independent samples *t* tests for normally distributed continuous variables and Mann–Whitney *U*-tests for non-normally distributed continuous variables. Categorical variables were analyzed using Pearson's chi-squared test or Fisher's exact test. For longitudinal outcomes, distributional assumptions for repeated-measures ANOVA were assessed. Normality was assessed using the Shapiro–Wilk test, and sphericity was examined using Mauchly's test. Two-way repeated-measures ANOVA was applied for data satisfying both normality and sphericity assumptions (NRS scores), whereas generalized estimating equations (GEE) were used for variables violating these assumptions (QoR-15 scores). Simple effects with Bonferroni correction were performed for between-group comparisons at each time point. Statistical significance was defined as a two-sided $P < 0.05$.

The Hodges–Lehmann estimator was used to calculate the median difference with its 95% confidence interval (CI). All statistical analyses were performed using SPSS (version 26.0; IBM SPSS, Chicago, IL, USA) and R software (version 3.5.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

Study Population

From May 2025 to October 2025, a total of 313 patients were assessed for eligibility. Of these, 65 patients were excluded, and 248 patients were randomly (1:1) assigned to either the oliceridine or the sufentanil group. One patient in the oliceridine group was lost to follow-up, per-protocol analysis ultimately included 123 patients in the oliceridine group and 124 in the sufentanil group, as shown in the CONSORT-adherent flowchart (Figure 1). Baseline characteristics and perioperative data were comparable between groups (Table 1).

Primary Outcome

Within the first 3 PODs, a higher proportion of patients achieved SAME in the oliceridine group than in the sufentanil group (46.3% vs 32.3%; absolute difference = 14.1%, 95% CI: 2.0 to 26.1; relative increase 44%; $P = 0.023$; NNT = 7). On POD1 and POD2, the oliceridine group also demonstrated higher SAME rates, with absolute differences of 14.9% (95% CI: 2.8 to 27.1; $P = 0.017$) and 14.2% (95% CI: 2.0 to 26.4; $P = 0.024$), respectively (Table 2).

Secondary Outcomes

The oliceridine group displayed significantly lower NRS scores on POD1 (3.6 ± 1.9 vs 4.4 ± 2.1 ; mean difference, -0.7 ; 95% CI, -1.3 to -0.1 ; $P = 0.018$) and POD2 (3.2 ± 1.2 vs 3.7 ± 1.3 ; mean difference, -0.4 ; 95% CI, -0.7 to -0.1 ; $P = 0.039$). On POD3, no significant difference was observed between the two groups (2.3 ± 0.8 vs 2.5 ± 0.9 ; mean difference, -0.2 ; 95% CI, -0.5 to 0.1 ; $P > 0.05$) (Table 3 and Figure 2a).

Within the first 3 PODs, the oliceridine group required fewer PCIA boluses (9 [8, 12] vs 11 [8, 13]; $P = 0.030$) and had a lower incidence of rescue analgesia (4.1% vs 12.1%; $P = 0.021$) compared to the sufentanil group (Table 3). The incidence of nausea was lower in the oliceridine group than in the sufentanil group (12.2% [15/123] vs 24.2% [30/124]; $P = 0.015$). A lower incidence of vomiting was also observed in the oliceridine group, but with no statistical difference between groups (5.7% [7/123] vs 10.5% [13/124]; $P = 0.167$) (Figure 2b).

The oliceridine group exhibited significantly higher QoR-15 scores on POD1 (125 [123, 128] vs 118 [116, 121]; median difference = 7; 95% CI: 4 to 9; $P < 0.001$) and POD2 (133 [129, 137] vs 128 [125, 131]; median difference = 5; 95% CI: 1 to 8;

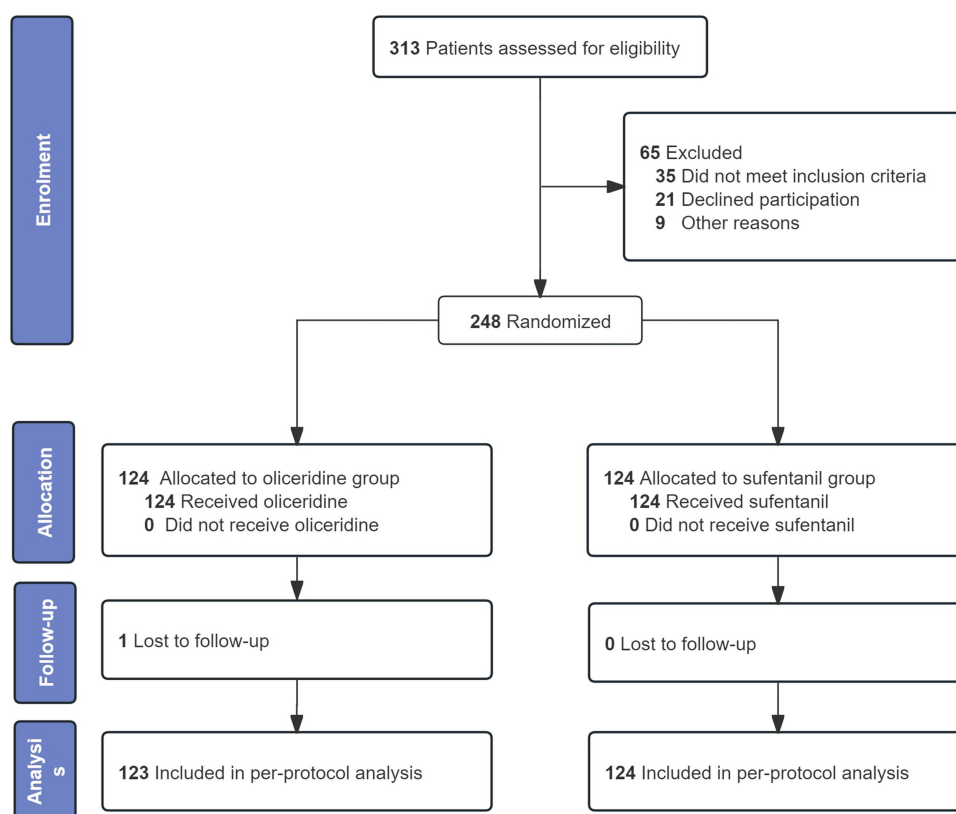


Figure 1 Study flow diagram.

$P = 0.010$). In addition, time to ambulation was significantly shorter in the oliceridine group (19 h [16, 22] vs 22 h [18, 25]; median difference = -3 h; 95% CI: -4 to -2 ; $P < 0.001$). No significant differences were observed between the two groups in time to chest tube removal, postoperative length of stay, or patient satisfaction scores (Tables 3 and 4).

Table 1 Baseline and Perioperative Characteristics

	Oliceridine Group (n = 123)	Sufentanil Group (n = 124)	P value
Age, yr	70 (67, 73)	69 (67, 72)	0.291
Female, n (%)	69 (56.1)	72 (58.1)	0.755
BMI, kg/m ²	24.2 ± 3.2	23.9 ± 3.0	0.448
ASA physical status, II/III	80/43	84/40	0.653
Preoperative comorbidities, n (%)	80 (65.0)	86 (69.4)	0.470
Hypertension	58 (47.2)	63 (50.8)	
Diabetes mellitus	25 (20.3)	15 (12.1)	
Coronary artery disease	11 (8.9)	18 (14.5)	
Anemia	14 (11.4)	12 (9.7)	
History of stroke	16 (13)	11 (8.9)	
History of malignancy	10 (8.1)	9 (7.3)	
Other comorbidities	7 (5.7)	14 (11.3)	
Smoking, n (%)	24 (19.5)	26 (21.0)	0.776
Preoperative lung function			
Predicted percentages of FVC, %	97 (86, 106)	96 (83, 101)	0.286
MVV < 80% predicted, n (%)	19 (15.4)	15 (12.1)	0.445

(Continued)

Table 1 (Continued).

	Oliceridine Group (n = 123)	Sufentanil Group (n = 124)	P value
FEV1 to FVC ratio < 80%, n (%)	8 (6.5)	5 (4.0)	0.384
Type of pulmonary resection, n (%)			
Lobectomy/Segmentectomy	80/43	74/50	0.384
Side of surgery, left/right	45/78	49/75	0.635
Duration of surgery, min	91 (71, 140)	95 (64, 119)	0.488
Duration of anesthesia, min	112 (94, 155)	110 (76, 140)	0.395
Intraoperative opioid consumption			
Sufentanil, µg	48.8 ± 8.9	50.2 ± 9.4	0.231
Remifentanil, µg	889.5 ± 357.5	871.1 ± 362.1	0.688
Total fluid infusion, mL	1300 (1150, 1400)	1300 (1050, 1450)	0.787
Urine output, mL	250 (200, 400)	220 (150, 500)	0.262
Estimated blood loss, mL	50 (30, 60)	50 (20, 80)	0.691
Indicators in recovery period			
Length of PACU stay, min	60.2 ± 28.3	62.8 ± 31.2	0.493
Time of extubation, min	28.3 ± 14.5	26.6 ± 12.7	0.328
Need for rescue analgesics in PACU, n (%)	2 (1.6)	4 (3.2)	0.684
Need for rescue antiemetics in PACU, n (%)	1 (0.8)	2 (1.6)	1.000

Notes: Data are presented as mean ± SD, median (Quartile 1, Quartile 3), or n (%). All analyses were performed on a per-protocol basis.

Abbreviations: ASA, American Society of Anesthesiologists; FVC, forced vital capacity; MVV, maximal voluntary ventilation; FEV1, forced expiratory volume in 1 s; PACU, postanesthesia care unit.

Table 2 Achievement of SAME and Related Outcomes Within the First 3 Postoperative days

	Oliceridine Group (n = 123)	Sufentanil Group (n = 124)	Absolute Difference (95% CI)	P value
SAME within the first 3 PODs, n (%)	57 (46.3)	40 (32.3)	14.1 (2.0 to 26.1)	0.023*
SAME on POD 1, n (%)	60 (48.8)	42 (33.9)	14.9 (2.8 to 27.1)	0.017*
SAME on POD 2, n (%)	79 (64.2)	62 (50.0)	14.2 (2.0 to 26.4)	0.024*
SAME on POD 3, n (%)	114 (92.7)	111 (89.5)	3.2 (−3.9 to 10.3)	0.382
POD 1–3 NRS scores < 4 on cough, n (%)	60 (48.8)	41 (33.1)	15.7 (0.9 to 30.5)	0.012*
POD 1–3 PONV scores < 2, n (%)	114 (92.7)	108 (87.1)	5.6 (−3.6 to 14.7)	0.197

Notes: Data are presented as n (%). All analyses were performed on a per-protocol basis. *P < 0.05.

Abbreviations: SAME, satisfactory analgesia with minimal emesis; POD, postoperative day; NRS, numerical rating scale; PONV, postoperative nausea and vomiting; CI, confidence interval.

Table 3 Postoperative NRS Scores, PCIA Utilization and Patient Satisfaction Scores on PCIA

	Oliceridine Group (n = 123)	Sufentanil Group (n = 124)	Mean or Median Difference (95% CI)	P value
NRS scores during coughing				
POD 1	3.6 ± 1.9	4.4 ± 2.1	−0.7 (−1.3 to −0.1)	0.018*
POD 2	3.2 ± 1.2	3.7 ± 1.3	−0.4 (−0.7 to −0.1)	0.039*
POD 3	2.3 ± 0.8	2.5 ± 0.9	−0.2 (−0.5 to 0.1)	0.238
Time to the first PCIA bolus, h	1.5 (0.4, 3.9)	1.6 (0.5, 3.2)	−0.1 (−0.7 to 0.5)	0.526
Number of PCIA boluses, times	9 (8, 12)	11 (8, 13)	−2 (−3 to −1)	0.030*
Rescue analgesia, n (%)	5 (4.1)	15 (12.1)	−8.0 (−14.8 to −1.2)	0.021*
Patient satisfaction scores	5 (4, 5)	5 (4, 5)	0 (−1 to 1)	0.329

Notes: Data are presented as mean ± SD, median (Quartile 1, Quartile 3), or n (%). All analyses were performed on a per-protocol basis. *P < 0.05.

Abbreviations: NRS, numerical rating scale; POD, postoperative day; PCIA, patient-controlled intravenous analgesia; CI, confidence interval.

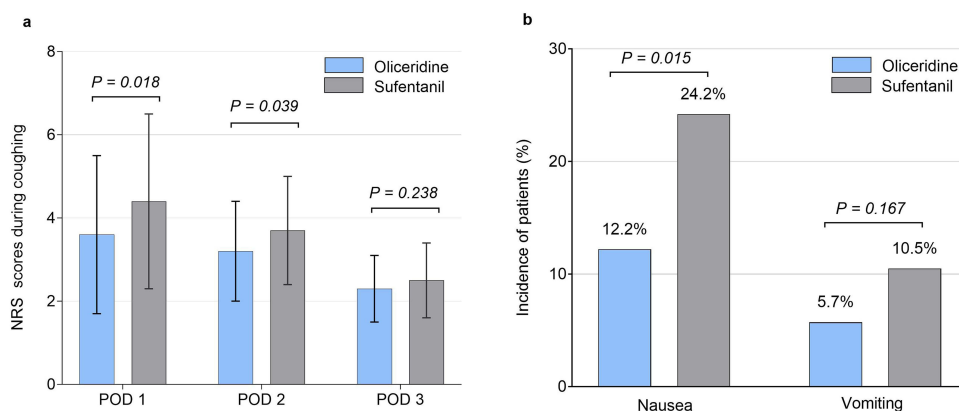


Figure 2 The numerical rating scale (NRS) scores and incidence of nausea and vomiting within the first 3 postoperative days (PODs). (a) NRS scores, Data are presented as mean \pm SD; (b) incidence of nausea and vomiting, Data are presented as n (%).

Safety Outcomes

The incidences of constipation (24 [19.5%] and 21 [16.9%]), dizziness (16 [13.0%] vs 18 [14.5%]), pruritus (6 [4.9%] vs 4 [3.2%]), and urinary retention (3 [2.4%] vs 1 [0.8%]) were similar between the oliceridine and sufentanil groups, with no statistically significant differences. Additionally, one case (0.8%) of severe sedation was reported in the oliceridine group, and one case (0.8%) of severe respiratory depression occurred in the sufentanil group (Table 5).

Table 4 Postoperative Recovery

	Oliceridine Group (n = 123)	Sufentanil Group (n = 124)	Median Difference (95% CI)	P value
QoR-15 scores				
POD1	125 (123, 128)	118 (116, 121)	7 (4 to 9)	< 0.001***
POD2	133 (129, 137)	128 (125, 131)	5 (1 to 8)	0.010*
POD3	136 (133, 138)	134 (132, 137)	2 (-1 to 5)	0.420
Time to ambulation, h	19 (16, 22)	22 (18, 25)	-3 (-4 to -1)	< 0.001***
Chest tube duration, d	3 (2, 3)	3 (2, 3)	0 (-1 to 0)	0.432
Postoperative length of stay, d	4 (3, 5)	4 (3, 5)	0 (-1 to 0)	0.135

Notes: Data are presented as median (Quartile 1, Quartile 3). All analyses were performed on a per-protocol basis. * $P < 0.05$, *** $P < 0.001$.

Abbreviations: QoR-15, 15-item Quality of Recovery scale; POD, postoperative day; CI, confidence interval.

Table 5 Safety Outcomes

	Oliceridine Group (n = 123)	Sufentanil Group (n = 124)	Absolute Difference (95% CI)	P value
Constipation, n (%)	24 (19.5)	21 (16.9)	2.6 (-7.0 to 12.2)	0.600
Dizziness, n (%)	16 (13.0)	18 (14.5)	-1.5 (-10.1 to 7.1)	0.731
Pruritus, n (%)	6 (4.9)	4 (3.2)	1.7 (-3.3 to 6.6)	0.510
Urinary retention, n (%)	3 (2.4)	1 (0.8)	1.6 (-1.5 to 4.8)	0.309
Severe sedation ^a , n (%)	1 (0.8)	0	NA	1.000
Severe respiratory depression ^b , n (%)	0	1 (0.8)	NA	1.000

Notes: Data are presented as n (%). All analyses were performed on a per-protocol basis. ^aDefined as responds only after shaking (No response to verbal stimuli); ^bDefined as oxygen saturation of \leq 90%, accompanied by the need for supportive airway management.

Abbreviation: CI, confidence interval.

Discussion

In this randomized clinical study, we firstly showed oliceridine provided a 44% relative increase over sufentanil in the proportion of elderly patients achieving SAME within 3 PODs following thoracoscopic lung surgery, underscoring its superior benefits in balance analgesia and side effects.

Post-VATS pain is notably exacerbated by chest wall-stretching movements like coughing, primarily due to intercostal nerve injury or chest tube irritation, which can lead to pulmonary complications and delayed recovery.² While traditional opioids like sufentanil are effective, their utility is limited by a high incidence of PONV.^{24,25} Considering the unique challenges of post-thoracotomy pain and the adverse event profile of opioids, our study focused on the proportion of SAME. The proportion of patients achieving SAME within the first 3 PODs was 32.3% in the sufentanil group, which is consistent with prior report,²⁰ whereas the oliceridine group showed a significant increase, with a SAME proportion of 46.3% primarily attributed to its superior analgesic efficacy. Notably, oliceridine reduced moderate-to-severe cough-related pain and rescue analgesia requirements. This finding contrasts with some evidence suggesting oliceridine is not superior^{26,27} or is even inferior²⁸ to sufentanil. This discrepancy may be attributed to our specific focus on cough-related pain, which reflects visceral and stretch-sensitive nociception. This interpretation is supported by Meng et al,²⁹ who reported that oliceridine effectively reduced NRS scores during coughing after thoracoscopic surgery, despite no difference in resting pain. The shorter context-sensitive half-time and linear pharmacokinetics of oliceridine likely contribute to more stable plasma concentrations,³⁰ reducing the risk of pain exacerbations. Nonetheless, large-scale, multicenter trials are needed to confirm whether oliceridine provides superior efficacy specifically against visceral pain.

Our findings confirm the superior gastrointestinal tolerability of oliceridine, with the incidence of PONV halved compared to the sufentanil group, a trend similarly observed in a recent study.^{23,28} This effect can be explained by the reduced recruitment of β -arrestin in enteric neurons by oliceridine.¹⁵ Notably, the PONV incidence was higher in their study than in our cohort. Additionally, no significant difference was observed in the incidence of moderate-to-severe nausea and vomiting (PONV score ≥ 2) between oliceridine and sufentanil in our study. These differences may be attributed to the fact that most of patients were not at high risk for PONV, perioperative prophylactic antiemetics, and application of multimodal analgesia.

Previous studies have reported that oliceridine could improve QoR-15 scores at 24 h postoperatively²⁹ and shorten the time to first flatus in patients undergoing laparoscopic hysterectomy.²⁶ Consistent with these findings, our study demonstrated higher QoR-15 scores in the oliceridine group on POD1 and POD2, with median differences of 7 and 5, respectively. As the minimal clinically important difference for QoR-15 is 6.0,³¹ the improvement in quality of recovery was clinically meaningful on POD1. This benefit may be attributable to better analgesia, fewer opioid-related adverse events, and earlier ambulation. Despite earlier ambulation and higher QoR-15 were observed in Oliceridine group, the postoperative length of stay shown no different, which may be attributed to the consistent duration of chest tube placement and the standardized hospital discharge protocol.

The incidence of safety outcomes was comparable between groups in this study. Among these, opioid-induced respiratory depression is the primary concerned in clinical practice. It was reported that 23% of patients receiving oliceridine-based PCIA experienced respiratory compromise events,²¹ and compared with sufentanil, oliceridine reduced the incidence of respiratory depression in gastrointestinal endoscopy.²³ However, recent studies suggested that oliceridine did not reduce the risk of opioid-induced respiratory depression compared to conventional opioids.^{26,27} In our study, no severe respiratory events occurred in the oliceridine group. These inconsistency between studies may due to the differences in the patients enrolled and evaluation indicators.

The findings of this study provide valuable insights for the development of drugs targeting biased μ -opioid receptor signaling pathways. In elderly patients undergoing VATS, oliceridine achieves effective analgesia while producing minimal opioid-related emesis, supporting its potential to dissociate analgesic effects from adverse side effects. Future research can focus on developing agonists with higher selectivity and evaluating their benefits in vulnerable patients at high risk of nausea, vomiting, respiratory depression and oversedation,³² as well as integrating biased agonists into multimodal analgesic regimens to optimize pain management and reduce opioid-related complications.

This study has several limitations. The observed treatment effect (14.1% absolute difference) in our study might be smaller than the anticipated 20% absolute difference from our pilot study, and consequently, further studies are needed to confirm the clinical effectiveness of this analgesic strategy. Second, the study only evaluated NRS scores during coughing, as defined by the SAME endpoint, and did not assess NRS scores at rest. Third, chronic pain after VATS also requires attention; however, we only evaluated the efficacy of oliceridine in acute pain treatment and did not address its impact on chronic pain. Finally, the single-center design may limit the generalizability of our findings.

Conclusion

In elderly patients undergoing thoracoscopic lung resection, oliceridine was associated with a higher proportion of achieving SAME within the first 3 PODs and improved early recovery outcomes as evidenced by higher QoR-15 scores, earlier ambulation, and reduced rescue analgesia needs, with no compromise to safety. These findings support oliceridine as a valuable and well-tolerated opioid option within multimodal analgesic strategies for this population, offering effective pain control while meaningfully reducing PONV.

Data Sharing Statement

The study data can be provided by contacting the corresponding author (njmu528@163.com; Heliang Sun) on reasonable request.

Ethics Approval and Consent to Participate

This study was approved by The First Affiliated Hospital of Nanjing Medical University (2024-SR-793), and written informed consents were obtained from all patients.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the National Natural Science Foundation of China (Grant No. 82371283).

Disclosure

The authors declare no conflict of interest.

References

- Hu JH, Zhong ZZ, Shi HJ, et al. Esketamine vs. placebo combined with erector spinae plane block vs. intercostal nerve block on quality of recovery following thoracoscopic lung resection: a randomized controlled factorial trial. *Int J Surg.* 2025;111(1):677–685. doi:10.1097/JS9.0000000000002060
- Batchelor TJP, Rasburn NJ, Abdelnour-Berchtold E, et al. Guidelines for enhanced recovery after lung surgery: recommendations of the Enhanced Recovery After Surgery (ERAS[®]) Society and the European Society of Thoracic Surgeons (ESTS). *Eur J Cardiothorac Surg.* 2019;55(1):91–115. doi:10.1093/ejcts/ezy301
- Yan X, Liang C, Jiang J, Ji Y, Wu AS, Wei CW. Effects of balanced opioid-free anesthesia on post-operative nausea and vomiting in patients undergoing video-assisted thoracic surgery: a randomized trial. *BMC Anesthesiol.* 2025;25(1):62. doi:10.1186/s12871-025-02938-x
- Zhang A, Zhou Y, Zheng X, et al. Effects of S-ketamine added to patient-controlled analgesia on early postoperative pain and recovery in patients undergoing thoracoscopic lung surgery: a randomized double-blinded controlled trial. *J Clin Anesth.* 2024;92:111299. doi:10.1016/j.jclinane.2023.111299
- Tong Y, Wei P, Wang S, et al. Characteristics of postoperative pain after VATS and pain-related factors: the experience in National Cancer Center of China. *J Pain Res.* 2020;13:1861–1867. doi:10.2147/JPR.S285650
- Lee W, Gao X, Tang J, et al. Postoperative sufentanil intravenous patient-controlled analgesia within the first 24 hours: a retrospective study. *Ann Palliat Med.* 2020;9(6):3932–3937. doi:10.21037/apm-20-1939
- Wick EC, Grant MC, Wu CL. Postoperative multimodal analgesia pain management with nonopioid analgesics and techniques: a review. *JAMA Surg.* 2017;152(7):691–697. doi:10.1001/jamasurg.2017.0898

8. Razi SS, Stephens-McDonnough JA, Haq S, et al. Significant reduction of postoperative pain and opioid analgesics requirement with an enhanced recovery after thoracic surgery protocol. *J Thorac Cardiovasc Surg.* 2021;161(4):1689–1701. doi:10.1016/j.jtcvs.2019.12.137
9. Feng X, Yang P, Liao Z, Zhou R, Chen L, Ye L. Comparison of oxycodone and sufentanil in patient-controlled intravenous analgesia for postoperative patients: a meta-analysis of randomized controlled trials. *Chin Med J.* 2023;136(1):45–52. doi:10.1097/CM9.0000000000002259
10. Feng CD, Xu Y, Chen S, et al. Opioid-free anaesthesia reduces postoperative nausea and vomiting after thoracoscopic lung resection: a randomized controlled trial. *Br J Anaesth.* 2024;132(2):267–276. doi:10.1016/j.bja.2023.11.008
11. Zhang YE, Xu X, Gong R. Postoperative pain management outcomes at a Chinese hospital: a cross-sectional survey. *J Perianesth Nurs.* 2023;38(3):434–439. doi:10.1016/j.jopan.2022.07.002
12. Nicholson BD. Economic and clinical burden of opioid-induced nausea and vomiting. *Postgrad Med.* 2017;129(1):111–117. doi:10.1080/00325481.2017.1243004
13. Aceto P, Antonelli Incalzi R, Bettelli G, et al. Perioperative Management of Elderly patients (PriME): recommendations from an Italian intersociety consensus. *Aging Clin Exp Res.* 2020;32(9):1647–1673. doi:10.1007/s40520-020-01624-x
14. Boitor M, Ballard A, Emed J, et al. Risk factors for severe opioid-induced respiratory depression in hospitalized adults: a case-control study. *Can J Pain.* 2020;4(1):103–110. doi:10.1080/24740527.2020.1714431
15. Simons P, van der Schrier R, van Lemmen M, et al. Respiratory effects of biased ligand oliceridine in older volunteers: a pharmacokinetic-pharmacodynamic comparison with morphine. *Anesthesiology.* 2023;138(3):249–263. doi:10.1097/ALN.0000000000004473
16. Beard TL, Michalsky C, Candiotti KA, et al. Oliceridine is associated with reduced risk of vomiting and need for rescue antiemetics compared to morphine: exploratory analysis from two Phase 3 randomized placebo and active controlled trials. *Pain Ther.* 2021;10(1):401–413. doi:10.1007/s40122-020-00216-x
17. DeWire SM, Yamashita DS, Rominger DH, et al. A G protein-biased ligand at the μ -opioid receptor is potently analgesic with reduced gastrointestinal and respiratory dysfunction compared with morphine. *J Pharmacol Exp Ther.* 2013;344(3):708–717. doi:10.1124/jpet.112.201616
18. Gan TJ, Wase L. Oliceridine, a G protein-selective ligand at the μ -opioid receptor, for the management of moderate to severe acute pain. *Drugs Today.* 2020;56(4):269–286. doi:10.1358/dot.2020.56.4.3107707
19. Shanthanna H, Paul J, Lovrics P, et al. Satisfactory analgesia with minimal emesis in day surgeries: a randomised controlled trial of morphine versus hydromorphone. *Br J Anaesth.* 2019;122(6):e107–e113. doi:10.1016/j.bja.2019.03.036
20. Yu H, Tian W, Xu Z, et al. Patient-controlled intravenous analgesia with opioids after thoracoscopic lung surgery: a randomized clinical trial. *BMC Anesthesiol.* 2022;22(1):253. doi:10.1186/s12871-022-01785-4
21. Sessler DI, Ayad S, Bakal O, et al. Oliceridine for postoperative pain and opioid-related complications: the intravenous oliceridine and opioid-related complications (VOLITION) prospective cohort study. *J Clin Anesth.* 2025;105:111870. doi:10.1016/j.jclinane.2025.111870
22. Raff M, Belbachir A, El-Tallawy S, et al. Intravenous oxycodone versus other intravenous strong opioids for acute postoperative pain control: a systematic review of randomized controlled trials. *Pain Ther.* 2019;8(1):19–39. doi:10.1007/s40122-019-0122-4
23. Ma B, Li Y, Leng C, et al. A comparative evaluation of the safety and efficacy of oliceridine and sufentanil in gastrointestinal endoscopy: a single-center, randomized controlled trial. *Drug Des Devel Ther.* 2025;19:5111–5121. doi:10.2147/DDDT.S512529
24. Chen J, Tu Q, Miao S, Zhou Z, Hu S. Transcutaneous electrical acupoint stimulation for preventing postoperative nausea and vomiting after general anesthesia: a meta-analysis of randomized controlled trials. *Int J Surg.* 2020;73:57–64. doi:10.1016/j.ijsu.2019.10.036
25. Wang D, Long YQ, Sun Y, et al. Opioid-free total intravenous anesthesia for thyroid and parathyroid surgery: protocol for a randomized, double-blind, controlled trial. *Front Med.* 2022;9:939098. doi:10.3389/fmed.2022.939098
26. Ke Z, He Y, Hu Q, Zheng D, Yao Z, Zhou W. A comparison of the effects of oliceridine and sufentanil on the quality of recovery after hysteroscopic surgery: a prospective double-blind randomized controlled trial. *J Anesth.* 2025. doi:10.1007/s00540-025-03578-8
27. Huang C, Liu B, Xie S, et al. Evaluating The opioid-related adverse events of oliceridine versus conventional opioids in patient-controlled analgesia after thoracoscopic lung resection: a retrospective cohort study. *Drug Des Devel Ther.* 2025;19:5929–5939. doi:10.2147/DDDT.S532778
28. Tian Y, Hu J, Pan H, Bai G, Zhang Z, Zhang P. Effect of oliceridine combined with sufentanil on patient-controlled intravenous analgesia in elderly patients after laparoscopic radical resection of rectal cancer: a prospective randomized controlled study. *Drug Des Devel Ther.* 2025;19:10033–10043. doi:10.2147/DDDT.S553848
29. Meng Y, Yuan S, Zhang H, et al. Comparison of oliceridine and sufentanil in patient-controlled intravenous analgesia for post-thoracoscopic nausea and vomiting: a prospective, double-blind, randomized controlled trial. *Front Pharmacol.* 2025;16:1576154. doi:10.3389/fphar.2025.1576154
30. Markham A. Oliceridine: first approval. *Drugs.* 2020;80(16):1739–1744. doi:10.1007/s40265-020-01425-6
31. Myles PS, Myles DB. An Updated Minimal Clinically Important Difference for the QoR-15 Scale. *Anesthesiology.* 2021;135(5):934–935. doi:10.1097/ALN.0000000000003977
32. Moss L, Hijma H, Demitrack M, et al. Neurocognitive effect of biased μ -opioid receptor agonist oliceridine, a utility function analysis and comparison with morphine. *Anesthesiology.* 2023;139(6):746–756. doi:10.1097/ALN.0000000000004758

Drug Design, Development and Therapy

Publish your work in this journal

Drug Design, Development and Therapy is an international, peer-reviewed open-access journal that spans the spectrum of drug design and development through to clinical applications. Clinical outcomes, patient safety, and programs for the development and effective, safe, and sustained use of medicines are a feature of the journal, which has also been accepted for indexing on PubMed Central. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/drug-design-development-and-therapy-journal>

Dovepress
Taylor & Francis Group